Amendments to the Specification:

Please replace the paragraph beginning at page 1, line 4, with the following redlined paragraph:

This application is a CIP of U.S. Application No. 09/684,361, filed October 6, 2000, which is a CIP of U.S. Application No. 09/276,484, filed March ~~21~~25, 1999, which is a CIP of U.S. Application No. 09/164,223, filed September 30, 1998, all applications incorporated herein by reference in their entirety~~and are incorporated herein in entirety~~.

Amendments to the Abstract:

Please replace the original Abstract with the following redlined Abstract:

Compositions and methods for the therapy of malignant diseases, such as leukemia and cancer, are disclosed. Particularly, disclosed herein are methods for enhancing or inducing an immune response using compositions comprising a WT1 polypeptide.~~The compositions comprise one or more of a WT1 polynucleotide, a WT1 polypeptide, an antigen-presenting cell presenting a WT1 polypeptide, an antibody that specifically binds to a WT1 polypeptide; or a T cell that specifically reacts with a WT1 polypeptide. Such compositions may be used, for example, for the prevention and treatment of metastatic diseases.~~

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-15. (Canceled)

16. (Currently Amended) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient a composition comprising:

(a) a WT1 polypeptide ~~that comprises~~consisting of an immunogenic portion of a native WT1~~ or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antibodies and/or T-cell lines or clones is not substantially diminished~~, wherein the polypeptide ~~comprises~~ consists of the polypeptide set forth in SEQ ID NO:2; and

(b) a physiologically acceptable carrier or excipient;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

17. (Canceled)

18. (Currently Amended) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient an immunogenic composition comprising:

(a) a WT1 polypeptide ~~that comprises~~consisting of an immunogenic portion of a native WT1~~ or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antibodies and/or T-cell lines or clones is not substantially diminished~~, wherein the polypeptide ~~comprises~~ consists of the polypeptide set forth in SEQ ID NO:2; and

(b) a non-specific immune response enhancer;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

19.-23. (Canceled)

24. (Currently Amended) A method for stimulating and/or expanding T cells in a mammal, comprising administering to a mammal a composition comprising, a WT1 polypeptide ~~comprising~~ consisting of the polypeptide set forth in SEQ ID NO:2 and a physiologically acceptable carrier or excipient, thereby stimulating and/or expanding T cells in a mammal.

25.-49. (Canceled)

50. (Currently Amended) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient an immunogenic composition comprising:

(a) An isolated polypeptide comprising a WT1 polypeptide wherein the WT1 polypeptide ~~consisting of an immunogenic portion of a native WT1, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with WT1-specific antisera and/or T-cell lines or clones is not substantially diminished, wherein the polypeptide~~ consists of no more than amino acids 1-249 of WT1 and ~~wherein said polypeptide~~ comprises the amino acid sequence set forth in SEQ ID NO:2; and

(b) a non-specific immune response enhancer, wherein the non-specific immune response enhancer preferentially enhances a $CD8^+$ T cell response in a patient;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

51. (Withdrawn) The method of claim 50, wherein the polypeptide consists of 4-16 consecutive amino acids of WT1 and comprises at least a portion of SEQ ID NO:2.

52. (Withdrawn) The method of claim 50, wherein the polypeptide consists of 8-10 consecutive amino acids of WT1 and comprises at least a portion of SEQ ID NO:2.

53.-55. (Canceled)

56. (New) A method for enhancing or inducing an immune response in a human patient, comprising administering to a patient an immunogenic composition comprising:

(a) an isolated polypeptide comprising a WT1 polypeptide wherein the WT1 polypeptide comprises amino acids 1-249 of WT1 and wherein the WT1 polypeptide does not comprise full-length WT1;

(b) a non-specific immune response enhancer, wherein the non-specific immune response enhancer preferentially enhances a $CD8^+$ T cell response in a patient;

and thereby enhancing or inducing an immune response specific for WT1 or a cell expressing WT1 in the human patient.

REMARKS

Reconsideration of the above-identified application is respectfully requested. Claims 16-18, 24, 47, 50 and 53 are presently under consideration in this case. With the above amendment, claims 17, 47-49, and 53-55 have been canceled. Claims 16, 18, 24, and 50 have been amended for purposes of clarity and to advance prosecution of this application. New claim 56 has been added. It is urged that support for the above amendments can be found throughout the specification as originally filed and that none of the amendments constitutes new matter. In particular, support for non-specific immune response enhancers that preferentially enhance CD8+ T cells can be found, for example, at page 39, line 28-page 40, line 8. Support for full-length WT1 can be found throughout the application, in particular at page 8, lines 9-10; Figure 1; and SEQ ID NO:319. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed in a related divisional, continuation and/or continuation-in-part application.

Rejection under 35 U.S.C. § 112, first paragraph (new matter)

Claims 47, 50 and 53 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Action asserts that there is no support in the specification for the recitation of "polypeptide consists of no more than amino acids 1-249 of WT1 and wherein said polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2". The Action contends that while the specification discloses the construct containing amino acids 1-249, it does not disclose smaller peptides that contain SEQ ID NO:2 as recited in the claims. Therefore, the Action concludes that this recitation is new matter.

Applicants respectfully traverse this rejection on the following grounds. Applicants submit that the courts have held that all that is required to comply with the written description requirement is that the specification **reasonably convey** to persons skilled in the art

that the inventor had possession of the subject matter claimed. (*In re* Edwards, 568 F.2d 1349, 1351, 196 USPQ 465, 467 (CCPA 1978) (emphasis added). Applicants submit that the specification clearly describes a variety of portions of WT1, for example, on page 15, lines 1 - 24, as follows:

> Within the context of the present invention, a WT1 polypeptide is a polypeptide that **comprises at least an immunogenic portion** of a native WT1 (*i.e.*, a WT1 protein expressed by an organism that is not genetically modified), or a variant thereof, as described herein. A WT1 polypeptide **may be of any length**, provided that it comprises at least an immunogenic portion of a native protein or a variant thereof. In other words, a WT1 polypeptide may be an oligopeptide (*i.e.*, consisting of a relatively small number of amino acid residues, such as 8-10 residues, joined by peptide bonds), a full length WT1 protein (*e.g.*, present within a human or non-human animal, such as a mouse) **or a polypeptide of intermediate size** (emphasis added).

The specification further describes a variety of immunogenic portions, including SEQ ID NO:2, at for example, page 16, lines 1 - 5:

> Certain immunogenic portions have one or more of the sequences recited within one or more of Tables II - XIV. Representative immunogenic portions include, but are not limited to, RDLNALLPAVPSLGGGG (human WT1 residues 6-22; SEQ ID NO:1), PSQASSGQARMFPNAPYLPSCLE (human and mouse WT1 residues 117-139; SEQ ID NOs: 2 and 3 respectively)...

As mentioned in the Action, the specification clearly describes N-terminal portion of WT1 (*e.g.*, amino acids 1-249) for example of page 52, line 23. Accordingly, Applicants submit that the skilled artisan would readily appreciate in light of this description that the Applicants were indeed in possession of the claimed methods using a WT1 polypeptide wherein the polypeptide consists of no more than amino acids 1-249 of WT1 and wherein said polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2. Therefore, Applicants submit that the recited WT1 polypeptide is not new matter. Applicants note that solely to advance prosecution, claims 47 and 53 have been canceled without prejudice and

without acquiescence to the rejections. Applicants respectfully request that the rejection of claim 50 under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 16-18, 47, 50, 53 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Action asserts the specification does not adequately describe the claimed variants of WT1.

Applicants respectfully traverse this rejection and submit that as described in Applicants' specification, SEQ ID NO:2 represents a WT1 peptide with motifs appropriate for binding to MHC class I and MHC class II. This peptide was identified using TSites HLA peptide binding prediction analyses (*e.g.*, see Table XLV) and was further shown to contain a naturally processed cytotoxic T cell epitope using *in vitro* T cell assays (see *e.g.*, Example 5, at page 113, line 27-page 114, line 8). Immunization with the p117-139 peptide was demonstrated by Applicants to elicit a proliferative T cell responses *in vivo* (*e.g.*, Example 3, at pages 56-58). Moreover, the WT1-specific T cells stimulated *in vivo* with SEQ ID NO:144, comprised in the polypeptide set forth in SEQ ID NO:2, were demonstrated, using a chromium release assay, to be capable of killing WT1 positive tumor cells, whereas no killing of WT1 negative tumor cells was observed (*e.g.*, and Example 5, at pages 112-114). Thus, Applicants have identified T cells specific for SEQ ID NO:2 that are capable of recognizing and lysing tumor cells expressing WT1.

Importantly, these WT1-specific T-cells identified by Applicants can be routinely isolated and used in the identification of the immunogenic variants of SEQ ID NO:2. For example, a series of variants of SEQ ID NO:2, having up to 3 amino acid substitutions, can be synthesized and compared with SEQ ID NO:2 in their ability to stimulate proliferation of the WT1-specific T-cells. As disclosed by Applicants, at page 17, lines 10-15:

> (T)he ability of a variant to react with antigen-specific antisera and/or T-cell lines or clones may be enhanced or unchanged, relative to the native polypeptide, or may be diminished by less than 50%, and preferably less than 20%, relative to

> the native polypeptide. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antisera and/or T-cells as described herein.

Applicants submit that the skilled artisan would readily understand, in light of Applicants' disclosure, the single identifying characteristic common to the claimed variants, *i.e.*, their ability to stimulate T cells specific for SEQ ID NO:2, and would further appreciate the routine nature of the techniques used in their identification. Thus, in view of Applicants specification, and the routine and art recognized approaches for the identification and evaluation of variants that are reactive with antigen-specific T-cells, the person of ordinary skill in the art would recognize that Applicants were indeed in possession of the presently claimed invention as of the filing date of the captioned application.

Notwithstanding the foregoing, and solely to advance prosecution, Applicants have amended 16, 18, and 50 to remove recitation of variants and have canceled claims 47 and 53. Applicants have made these amendments without prejudice or acquiescence and reserve the right to prosecute any subject matter modified and/or removed in a related divisional, continuation and/or continuation-in-part application. Accordingly, Applicants submit that the rejection has been obviated and respectfully request its withdrawal.

Rejection under 35 U.S.C. § 112, second paragraph (indefiniteness)

Claim 17 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for depending from canceled claim 1.

Applicants have canceled claim 17 without prejudice. Therefore, Applicants submit that the rejection has been obviated and respectfully request its withdrawal.

Claims Rejected Under 35 U.S.C. §§ 102(e) or 102(a)

Claims 16-18, 24, 47, 50, and 53 stand rejected under 35 U.S.C. § 102(e) or 102(a) as allegedly anticipated by Chada *et al.* (U.S. Patent 5,693,522) as evidenced by Berzofsky *et al.* (WO 94/21287). Chada *et al.* allegedly teaches a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are

administered to a patient and that said WT1 peptide is administered with a pharmaceutically acceptable carrier or a non-specific immune enhancer. Chada *et al.*, further allegedly teaches the use of peptides which induce T cell mediated responses wherein the art allegedly recognizes that such peptides can have less than 16 amino acids, allegedly as per the teachings of Berzofsky *et al.* Berzofsky *et al.* allegedly teaches a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are administered to a patient, and that the WT1 peptide is administered with a pharmaceutically acceptable carrier or non-specific immune enhancer. Berzofsky *et al.* allegedly further teaches the use of peptides which induce T cell mediated responses wherein the peptide can be the minimal peptide that can bind MHC.

Applicants respectfully traverse this rejection on the following grounds.

Applicants note that solely to advance prosecution, claims 47 and 53 have been canceled without prejudice and without acquiescence to the rejections. Applicants submit that the pending claims 16, 18, and 24 have been amended without acquiescence to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:2. Chada *et al.* merely lists WT1 as a potential "altered cellular component" that could be used to generate an immune response, without demonstrating that WT1 is capable of inducing an immune response, as is disclosed by Applicants. Chada *et al.* does not teach or suggest using a WT1 polypeptide consisting of the sequence set forth in SEQ ID NO:2, nor does Chada *et al.* teach or suggest that a WT1 peptide consisting of SEQ ID NO:2, or any WT1 peptide for that matter, would be capable of effectively eliciting an immune response. With regard to amended claim 50 and newly added claim 56, Applicants submit that nowhere does Chada *et al.* teach or suggest a WT1 polypeptide consisting of no more than amino acids 1-249 of WT1 and wherein said polypeptide comprises the amino acid sequence of SEQ ID NO:2, or a WT1 polypeptide comprising 1-249 wherein said WT1 polypeptide does not comprise full length WT1, let alone that such WT1 polypeptides would be capable of effectively eliciting a CD8+ T cell response. Applicants submit that each and every element of the claims is not found in the cited references. Thus, Applicants respectfully submit that Chada *et al.* does not anticipate the presently claimed subject matter even as evidenced by Berzofsky *et al.* Applicants submit that this ground for rejection has been obviated and respectfully request reconsideration and withdrawal of the rejection.

Claims Rejected Under 35 U.S.C. § 102(b)

Claims 16-18, 24, 47, 50, and 53 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Berzofsky *et al.* (WO 94/21287). As noted above, Berzofsky *et al.* allegedly teaches a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are administered to a patient, and that the WT1 peptide is administered with a pharmaceutically acceptable carrier or non-specific immune enhancer. Berzofsky *et al.* allegedly further teaches the use of peptides which induce T cell mediated responses wherein the peptide can be the minimal peptide that can bind MHC.

Applicants respectfully traverse this rejection on the following grounds.

Applicants reiterate that solely to advance prosecution, claims 47 and 53 have been canceled without prejudice and without acquiescence to the rejections. Applicants submit that the pending claims 16, 18, and 24 have been amended without acquiescence to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:2. Similar to Chada *et al,* Berzofsky *et al.* merely lists WT1 as a potential protooncogene that could be used to generate an immune response, without demonstrating that WT1 is capable of inducing an immune response, as is disclosed by Applicants. Further, Berzofsky *et al.* does not teach or suggest using a WT1 polypeptide consisting of the sequence set forth in SEQ ID NO:2, nor does this reference teach or suggest that a WT1 peptide consisting of SEQ ID NO:2 would be capable of effectively eliciting an immune response. With regard to amended claim 50 and newly added claim 56, Applicants submit that nowhere does Berzofsky *et al.* teach or suggest a WT1 polypeptide consisting of no more than amino acids 1-249 of WT1 and wherein said polypeptide comprises the amino acid sequence of SEQ ID NO:2, or a WT1 polypeptide comprising 1-249 wherein said WT1 polypeptide does not comprise full length WT1, let alone that such WT1 polypeptides would be capable of effectively eliciting a CD8+ T cell response. Thus, Applicants submit that each and every element of the claims is not found in the cited references. Accordingly, Applicants respectfully submit that Berzofsky *et al.* does not anticipate the presently claimed subject matter. Applicants submit that this ground for rejection has been obviated and respectfully request reconsideration and withdrawal of the rejection.

Claims Rejected Under 35 U.S.C. § 103(a)

Claims 16, 18, 24, 47, 50, and 53 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chada *et al.* (U.S. Patent 5,693,522) in view of Herlyn *et al.* (WO 95/29995). Chada *et al.* is discussed above. Herlyn *et al.* allegedly teaches a peptide that consists of no more than amino acids 1-249 of WT1 and comprises SEQ ID NO:2 wherein said peptide is immunogenic, *e.g.* that it induces antibodies.

Applicants respectfully traverse this rejection and again note that claims 47 and 53 have been canceled without prejudice or acquiescence. Applicants further reiterate that pending claim 16, 18, and 24 have been amended without acquiescence to specify that the claimed WT1 immunogenic portion consists of SEQ ID NO:2. Applicants' arguments to the Examiner's position under 35 U.S.C. sections 102(e) and 102(a) regarding Chada *et al.* and Berzofsky *et al.* are equally applicable in the context of this rejection under 35 U.S.C. 103(a). As set forth above, Chada *et al.* and Berzofsky *et al.* fail to teach the specific WT1 immunogenic portions presently claimed by Applicants. Likewise, Herlyn *et al.* fails to teach the specific WT1 immunogenic portions presently claimed. In view of this, Applicants respectfully submit that the cited references, taken either alone or in combination, cannot reasonably render obvious the presently claimed WT1 immunogenic portion consisting of SEQ ID NO:2, when the cited references offer no teaching or suggestion as to the existence and/or the identity of the now claimed immunogenic portion.

With regard to amended claim 50, Applicants submit that Herlyn *et al.* teach the use of a fragment of WT1 consisting of amino acids 1-181 as a tool to generate antibodies in mice. Nowhere does Herlyn *et al.* teach or even suggest that a WT1 polypeptide consisting of no more than amino acids 1-249 of WT1 wherein said polypeptide comprises the amino acid sequence of SEQ ID NO:2, or any portion of WT1 for that matter, would be capable of effectively eliciting a CD8+ T cell response. Moreover, nowhere does Herlyn *et al.* even suggest that it would be desirable to elicit a WT1-specific T cell response. With regard to newly added claim 56, nowhere do the cited references teach or suggest a WT1 polypeptide comprising 1-249

wherein said WT1 polypeptide does not comprise full length WT1, or that such a WT1 polypeptide would be capable of effectively eliciting a T cell response.

Even assuming *arguendo* that the cited references show elements of Applicants' invention, there is no motivation for a skilled artisan to combine the cited references in order to arrive at Applicants' claimed invention. As the Federal Circuit has recently reiterated, "virtually all inventions are combinations of old elements." Further, the Court noted that although an Examiner may often find every element of a claimed invention in the prior art, such a finding is insufficient to support a *prima facie* case of obviousness. To properly support a *prima facie* case of obviousness, the Examiner must show a motivation to combine the references. To this end, the Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *In re Rouffet,* 47 USPQ2d 1453, 1458 (Fed. Cir. 1998). Further, when an Examiner relies on the skill in the art, the Examiner must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *Id.* As noted by the Federal Circuit, if merely "a rote invocation [of the skill in the art] could suffice to supply motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance." *Id.* Applicants submit that the skilled artisan would have had no motivation to combine the cited references to arrive at Applicants' invention solely based on the listing of WT1 as an altered cellular component or a protooncogene and the use of a portion of WT1 to generate antibodies as a diagnostic tool.

Without motivation to combine the prior art references, a skilled artisan would select and combine elements from the prior art only by examining the problem in hindsight. The Federal Circuit has firmly rejected such hindsight reconstruction used to "pick and choose among isolated disclosures in the prior art" to arrive at Applicants' invention. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). To this end, Applicants submit that no specific reasoning has been given for a skilled artisan to combine the cited prior art references. Accordingly, Applicants submit that the cited prior art references support only a mere hindsight reconstruction of Applicants' invention.

In light of the above remarks, Applicants respectfully submit that the claimed invention is not obvious in view of the cited references and respectfully request reconsideration and withdrawal of the rejection.

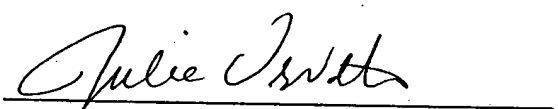
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Alexander Gaiger *et al.*

SEED Intellectual Property Law Group PLLC



Julie A. Urvater, Ph.D., Patent Agent
Registration No. 50,461

JAU:tt

Enclosure:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031
374776_1.DOC